SUMMARY OF PRODUCT CHARACTERISTICS
RANFERON CAPSULES
(Iron with Vitamins and Mineral Capsules)

1. **NAME OF THE MEDICINAL PRODUCT**

RANFERON CAPSULES

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains:
Ferrous Fumarate BP ....305 mg
(equivalent to elemental Iron 100 mg)
Folic Acid BP ....0.75 mg
Cyanocobalamin USP............5 mcg
Ascorbic Acid USP................75 mg
Zinc Sulfate BP..................... 5 mg
For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications 1, 2, 3, 4, 5, 6, 7, 8, 9

RANFERON CAPSULES are indicated for the treatment of anemia due to iron and folic acid deficiency.
RANFERON CAPSULES also contain useful quantities of cyanocobalamin, ascorbic acid and zinc, which help in red blood cell formation and function.

4.2 Posology and method of administration

Adults and adolescents:
One to two capsules can be taken daily in single or in two divided dosages or as directed by physician.

Contraindications 1, 2, 3, 4, 5, 6, 7, 10, 11

RANFERON CAPSULES are contraindicated in patients
• who are hypersensitive to iron, folic acid, vitamin B12, hydroxybenzoate esters, vitamin C, zinc, cobalt and other inactive ingredients of this formulation.
• with hemochromatosis, hemosiderosis and other iron overload syndromes.
• with untreated cobalamin deficiency. This can be untreated pernicious anaemia or other cause of cobalamin deficiency, including lifelong vegetarians. In elderly people, a cobalamin absorption test should be done before long-term folate therapy. Folate given to such patients for 3 months or longer has precipitated cobalamin neuropathy. No harm results from short courses of folate.
• receiving concomitant parenteral iron.
• receiving repeated blood transfusions.
• with folate dependent tumors.
• with malignant disease unless megaloblastic anemia due to folic acid deficiency.
• with paroxysmal nocturnal hemoglobinuria.

- with active peptic ulcer.
- with regional enteritis.
- with ulcerative colitis.

Special warnings and precautions for use

Warnings

Caution should be exercised when administering folic acid to patients who may have folate-dependent tumors.

Cyanocobalamin should not be used in patients with early Leber's disease (hereditary optic nerve atrophy), since rapid optic nerve atrophy has been reported following administration of the drug to these patients.

Precautions

Iron

Iron supplements should not be used for the treatment of anemias other than iron deficiency anemia. Treatment of iron deficiency anemia must only be undertaken under medical supervision. Those with elevated serum ferritin levels should be extremely cautious in the use of iron supplements.

Iron supplements can be highly toxic or lethal to small children. Those who use iron supplements should be kept away from children. Iron supplements should be used with extreme caution in those with chronic liver failure, alcoholic cirrhosis, chronic alcoholism and pancreatic insufficiency. Some post- gastrectomy patients show poor absorption of iron.

Iron should be used with caution in those with a history of gastritis, peptic ulcer disease, or gastrointestinal bleeding. Care is needed when treating patients with iron deficiency anemia with treated or controlled peptic ulceration.

The duration of treatment of uncomplicated iron deficiency anemia should not usually exceed 6 months (or 3 months after reversal of the anemia has been achieved).

Since anemia due to combined iron and vitamin B12 or folate deficiencies may be microcytic in type, patients with microcytic anemia resistant to therapy with iron alone should be screened for vitamin B12 or folate deficiency.

Folic acid

The use of folic acid doses above 1 mg/day may precipitate or exacerbate the neurological damage of vitamin B12 deficiency. Those who use folic acid doses above 1mg/day should only do so under medical supervision.

Those with undiagnosed anemia should exercise caution in the use of supplementary folic acid. Doses of folic acid greater than 100 mcg daily may result in hematologic improvement in those with vitamin B12 deficiency.

Folic acid should not be used in monotherapy in patients with pernicious anemia and other B12 deficiency states as this may lead to sub-acute combined degeneration of the spinal cord.

Cyanocobalamin
Allergic hypersensitivity reactions have occurred rarely after parenteral doses of the vitamin B12 compounds cyanocobalamin and hydroxocobalamin. Antibodies to hydroxocobalamin-transcobalamin II complex have developed during hydroxocobalamin therapy. Cyanocobalamin or hydroxocobalamin should, if possible, not be given to patients with suspected vitamin B12 deficiency without first confirming the diagnosis. Regular monitoring of the blood is advisable. Use of doses greater than 10 mcg daily may produce a hematological response in patients with folate deficiency; indiscriminate use may mask the precise diagnosis. Conversely, folate may mask vitamin B12 deficiency. Cyanocobalamin should not be used for Leber's disease or tobacco amblyopia since these optic neuropathies may degenerate further.

Ascorbic acid
Although oxalic acid is formed when ascorbic acid is metabolized, this is highly unlikely to cause renal problems in healthy individuals without pre-existing renal problems or who are not predisposed to increased crystal aggregation. Those with pre-existing kidney stone disease or a history of renal insufficiency defined as serum creatine greater than 2 and/or creatinine clearance less than 30, should exercise caution in the use of higher than RDA amounts of vitamin C. Ascorbic acid is involved in modulating iron absorption and transport. It is highly unlikely that healthy individuals who take supplemental vitamin C will have any problem with iron overload. On the other hand, those with hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia and erythrocyte G6PD deficiency might have such a problem if they use large amounts of vitamin C.

Zinc
Prolonged use of high doses of zinc supplements, by mouth or parenteral, leads to copper deficiency with associated sideroblastic anemia and neutropenia; full blood counts and serum cholesterol should be monitored to detect early signs of copper deficiency. Zinc toxicity has occurred after the use of contaminated water in hemodialysis solutions.
High serum zinc concentrations may be reduced by using a chelating drug such as sodium calcium edetate. Metal fume fever is an occupational disease associated with inhalation of freshly-oxidized metal fumes, most commonly from zinc, iron or copper. It is characterized by chills, fever, cough, dyspnea, myalgia, and chest pain, and is generally self-limiting and does not appear to be associated with long-term sequelae.

Interaction with other medicinal products and other forms of interaction
Iron

Iron reduces the absorption of penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) (give at least 2 hours apart), moxifloxacin, mycophenolate, norfloxacin, ofloxacin, zinc. Absorption of both iron and antibiotic may be reduced if iron is given with tetracycline. Absorption of oral iron is reduced by calcium salts.
Chloramphenicol delays plasma iron clearance, incorporation of iron into red blood cells and interferes with erythropoiesis. Some inhibition of iron absorption may occur if it is taken with cholestyramine, trientine, tea, coffee, eggs or milk.
Avoid concomitant use of iron with dimercaprol.
Oral iron antagonizes hypotensive effect of methyldopa.
Absorption of both iron and zinc are reduced if taken concomitantly.
Aluminum or magnesium containing antacids may decrease the absorption of iron if used concomitantly. The absorption iron salts is enhanced by ascorbic acid and meat.

Folic acid
Folic Acid has been observed to reduce plasma levels of anticonvulsants, particularly phenytoin and primidone; and therefore, patients should be carefully monitored by the physician and the anticonvulsant drug dose adjusted as necessary.
Co-trimoxazole, chloramphenicol, aminopterin, pyrimethamine, or sulphonamides may interfere with folate metabolism. Sulphasalazine can reduce the absorption of folic acid. Folic acid may interfere with the toxic and therapeutic effects of methotrexate. Folate supplements enhance the efficacy of lithium therapy. Methotrexate and trimethoprim are specific anti-folates and the folate deficiency caused by their prolonged use cannot be treated by folic acid. Folinic acid should be used. Nitrous oxide anaesthesia may cause an acute folic acid deficiency. Both ethanol and aspirin increase folic elimination.

Cyanocobalamin
Absorption of vitamin B12 from the GI tract may be decreased by aminoglycoside antibiotics, colchicine, extended release potassium preparations, aminosalicylic acid and its salts, anticonvulsants (e.g., phenytoin, phenobarbital, primidone), cobalt irradiation of the small bowel, and by excessive alcohol intake lasting longer than 2 weeks.

Neomycin-induced malabsorption of vitamin B12 may be increased by concurrent administration of colchicine. Ascorbic acid may destroy substantial amounts of dietary vitamin B12 *in vitro*; this possibility should be considered when large doses of ascorbic acid are ingested within 1 hour of oral vitamin B12 administration.
Prednisone has been reported to increase the absorption of vitamin B12 and secretion of intrinsic factor in a few patients with pernicious anemia, but not in patients with partial or total gastrectomy. The clinical importance of these findings is unknown.

Concurrent administration of chloramphenicol and vitamin B12 reportedly may antagonize the hematopoietic response to vitamin B12 in vitamin B12 -deficient patients.
The hematologic response to vitamin B12 in patients receiving both drugs should be carefully monitored and alternate anti-infectives should be considered.
Serum concentrations may be decreased by concurrent use of oral contraceptives. Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations.

Ascorbic acid
Ascorbic acid may interact with desferrioxamine, hormonal contraceptives, fluphenazine and warfarin. Ascorbic acid may increase the absorption of iron in iron-deficiency states.

The intake of large doses of vitamin C used at the same time as aluminum-containing Antacids have been reported to increase urinary aluminum excretion, suggesting increased aluminum absorption from these antacids. However, this is not well documented.

Chronic use of high dose aspirin may lead to impaired vitamin C status.

Vitamin C may potentiate the antineoplastic activity of cisplatin, doxorubicin and paclitaxel. It may also help ameliorate the cardiotoxic effect of doxorubicin and the nephrotoxic effect of cisplatin. This is based on *in vitro* and animal studies. There is a concern by some researchers that supplemental doses of vitamin C may diminish the efficacy of some chemotherapeutic agents. Ascorbic acid may enhance 17 beta-estradiol inhibition of oxidized LDL formation.

Vitamin C used concomitantly with nonheme iron supplements may increase the uptake of iron. This may cause problems in those with high iron stores or with propensity for iron overload, such as those with hemochromatosis, sideroblastic anemia, sickle cell anemia, thalassemia and erythrocyte G6PD deficiency.

Laboratory tests: Ascorbic acid, a strong reducing agent, interferes with laboratory tests involving oxidation and reduction reactions. Falsely - elevated or false-negative test results may be obtained from plasma, feces, or urine samples depending on such factors as the dose of ascorbic acid and specific method used. High intakes of vitamin C may cause falsely elevated bilirubin values. Large intakes of vitamin C may cause falsely elevated urine and serum creatinine levels. However, this is not well documented. Large intakes of vitamin C may cause false positive glucose readings measured by copper reduction methods (e.g., Clinitest) and false negative glucose results as measured by the oxidase methods (e.g., Clinistix and Tes-Tape). Intakes of vitamin C greater than 1 gram daily may cause a false negative guaiac test.

Zinc
The absorption of zinc may be reduced by iron supplements, penicillamine, phosphorus- containing preparations, and tetracyclines. Zinc supplements reduce the absorption of copper, fluoroquinolones, iron, penicillamine and tetracyclines.

Concomitant intake of a bisphosphonate and zinc may decrease the absorption of both the bisphosphonate and zinc.
Foods rich in cysteine-containing proteins (e.g., animal muscle tissue) may increase the absorption of zinc if ingested concomitantly.

Concomitant intake of zinc with foods rich in oxalic acid (spinach, sweet potatoes, rhubarb and beans), foods rich in phytic acid (unleavened bread, raw beans, seeds, nuts and grains and soy isolates) may decrease the absorption of zinc.

Concomitant intake of tea (tannins), coffee, or caffeine and zinc may cause decreased absorption of zinc.

Fertility, Pregnancy and lactation
Pregnancy
Iron: It is recommended that iron supplements in tablet form be given to all pregnant women because of the difficulties in correctly assessing iron status in pregnancy. In non- anemic pregnant women, daily supplements of 100 mg of iron (e.g. as ferrous sulphate) given during the second half of pregnancy are adequate. In anemic women, higher doses
are usually required.
Pregnant women should not use supplemental doses of iron higher than Recommended
Daily Allowances (RDA) unless higher doses are recommended by their physicians.

Folic acid: There are no known hazards to the use of folic acid, indeed folic acid supplements are often necessary in pregnancy. Women of childbearing age and pregnant women should ensure that their intake of folic acid from nutritional supplements and/or fortified food is 400 mcg/day. A number of pre- and postnatal supplements deliver 1 mg (1,000 mcg) daily of folic acid. Doses higher than 1 mg/day should only be used by the above groups if prescribed by their physicians.

Cyanocobalamin: During pregnancy, nutrients travel from mother to fetus through the placenta. Vitamin B12, like other nutrients, is transferred across the placenta during pregnancy. Vitamin B12 deficiency in infants is rare but can occur as a result of maternal insufficiency. This is of particular concern because undetected and untreated vitamin B12 deficiency in infants can result in permanent neurologic damage.

Ascorbic acid: Pregnant women should avoid using supplemental doses of vitamin C higher than RDA amounts.

Zinc: Zinc plays many roles in pregnancy, and disturbances in zinc metabolism, as well as zinc deficiency, can have serious adverse effects on the course of pregnancy and upon the growth of the fetus and newborn. Zinc deficiency can be teratogenic, producing neural tube defects. Pregnant women should avoid zinc doses higher than RDA unless higher doses are recommended by their physicians.

Lactation

Iron: Iron secretion in milk and basal iron loss accounts for the iron loss in the lactating mother. Nursing mothers should not use supplemental doses of iron higher than

Recommended Daily Allowances unless higher doses are recommended by their physicians.

Folic acid: Folic acid is excreted in breast milk. Nursing mothers should ensure that their intake of folic acid from nutritional supplements and/or fortified food is 400 mcg/day. A number of pre- and postnatal supplements deliver 1 mg (1,000 mcg) daily of folic acid.

Doses higher than 1 mg/day should only be used by this group if prescribed by their physicians.

Cyanocobalamin: Vitamin B12 is distributed into breast milk. The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.

Breast-fed infants receive their nutrition, including vitamin B12, through breast milk. Vitamin B12 deficiency in infants is rare but can occur as a result of maternal insufficiency. For example, breast-fed infants of women who follow strict vegetarian diets have very limited reserves of vitamin B12 and can develop a vitamin B12 deficiency within months of birth. This is of particular concern because undetected and untreated vitamin B12 deficiency in infants can result in permanent neurologic damage. Consequences of such neurologic damage are severe and can be irreversible. Mothers who follow a strict vegetarian diet should consult with a pediatrician regarding appropriate use of vitamin B12 supplements for their infants and children. They should also discuss with their personal physician their own need for vitamin B12 supplements.

Ascorbic acid: Nursing mothers should avoid using supplemental doses of vitamin C higher than RDA amounts.

Zinc: Zinc is also very important to the newborn when breast milk may be its only source of zinc (during the first few months of life). Premature infants may be at even greater risk of zinc deficiency. Impaired disease resistance and diminished vaccine efficacy in infants may result from zinc deficiency at this stage. Some studies have shown that giving 15 milligrams of zinc daily to breast-feeding mothers produced more weight gain in their babies than in the babies of un-supplemented mothers. Zinc supplementation in infants not breast fed has also shown benefits.

Nursing mothers should avoid zinc doses higher than RDA unless higher doses are recommended by their physicians.

Effects on ability to drive and use machines

The effect of the drug on the ability to drive a car or work with other mechanisms has not been investigated.

Undesirable effects

Iron

The most common side effects are gastrointestinal ones and include nausea, vomiting, bloating and other abdominal discomfort, black stools, diarrhea, constipation and anorexia. Temporary staining of teeth occurs from iron-containing liquids. Oral iron, particularly modified release preparations, can exacerbate diarrhoea in patients with inflammatory bowel disease; care is also needed in patients with intestinal strictures and diverticular disease. Although iron preparations are best absorbed on an empty stomach, they may be taken after food to reduce gastrointestinal side-effects. Constipation may be caused by continual administration, particularly in older patients, and may lead to fecal impaction.

Hypersensitivity reactions have been reported. These range from rashes, sometimes severe, to anaphylaxis.

Iron supplementation may cause the blackening of stool.

Hypersensitivity reactions have been reported. These range from rashes, sometimes severe, to anaphylaxis.

Bronchial stenosis has been reported.

Iron preparations are a common cause of accidental overdose in children.

Folic acid

Allergic reactions, comprising erythema, rash, pruritus, urticaria, general malaise, dyspnea, and anaphylactic reactions (including shock) have been reported. Mild gastro-intestinal upsets such as anorexia, nausea, abdominal distention, flatulence, and a bitter/bad taste are rare but may occur. Morning sickness may occur in pregnancy but may be unrelated to the effects of folic acid.

Folic acid doses of up to 1 mg daily are well tolerated. There are more than 100 reported cases in which vitamin B12-deficient subjects who were receiving oral doses of folic acid of 5 mg daily or more experienced progression of neurological symptoms and signs.

There are very few such reports in those receiving doses of folic acid less than 5 mg daily. There are rare reports of hypersensitivity reactions to oral folic acid. There is one report of a trial using oral doses of folic acid of 15 mg daily for one month in which some subjects experienced sleep disturbances, mental changes and gastrointestinal effects.

Studies using comparable or higher doses, longer duration, or both, failed to confirm these findings.

Cyanocobalamin

Mild transient diarrhea, peripheral vascular thrombosis, itching, transitory exanthema, urticaria, feeling of swelling of the entire body, anaphylaxis, and death have been reported in patients receiving parenteral vitamin B12. Arrhythmias secondary to hypokalemia have occurred at the beginning of parenteral treatment with hydroxocobalamin.

Ascorbic acid

Ascorbic acid is usually nontoxic; however, nausea, vomiting, heartburn, abdominal cramps, fatigue, flushing, headache, insomnia, and sleepiness have been reported.
In healthy adults, oral doses up to 3 grams daily of vitamin C are unlikely to cause adverse reactions. The most common adverse reaction in those who take oral doses greater than 3 grams daily are gastrointestinal and include nausea, abdominal cramps, diarrhea and flatulent distention. These reactions are attributed to the osmotic effect of unabsorbed vitamin C passing through the intestine. Some advocates of megadose vitamin C use recommend titrating the daily dose of vitamin C to what they refer to as "bowel tolerance", i.e., the point at which the user begins experiencing diarrhea. This is not recommended. Rare adverse reactions reported in healthy individuals include: elevation of serum glucose, gastrointestinal obstruction, and esophagitis.
Other adverse effects reportedly associated with high vitamin C intake include diminished high-altitude tolerance, delayed-type allergic response, and erosion of dental enamel.

Zinc

Doses of zinc up to 30 milligrams daily are generally well tolerated. Higher doses may cause adverse reactions. The most common adverse reactions are gastrointestinal and include abdominal pain, dyspepsia, nausea, vomiting, diarrhea, gastric irritation, gastritis and gastrointestinal discomfort. Other adverse reactions include a metallic taste, headache and drowsiness. There are some reports of decreased HDL-cholesterol in those taking high doses of zinc. Chronic intake of high doses of zinc can lead to copper deficiency and hypochromic, microcytic anemia secondary to zinc-induced copper deficiency. High doses of zinc may be immunosuppressive.

Overdose 1, 2, 3, 4, 5, 6, 7, 11, 14

Iron

Ingestion of 20 mg/kg elemental iron is potentially toxic and 200-250 mg/kg is potentially fatal.
Acute iron overdosage can be divided into four stages. In the first phase, which occurs up to 6 hours after oral ingestion, gastrointestinal toxicity, notably vomiting, diarrhea and abdominal pain predominates. The vomit and stools may be grey or black. Other effects may include cardiovascular disorders such as hypotension and tachycardia, metabolic changes including acidosis and hyperglycemia, CNS depression ranging from lethargy to coma. Patients with only mild to moderate poisoning do not generally pass this first phase. The second phase may occur at 6-24 hours after ingestion and is characterized by a temporary remission or clinical stabilization. In the third phase gastrointestinal toxicity recurs together with shock (can result from hypovolemia or direct cardiotoxicity), metabolic acidosis, systemic toxicity, convulsions, coma, encephalopathy, hepatic necrosis and jaundice, hypoglycemia, coagulation disorders, oliguria or renal failure, poor tissue perfusion and pulmonary edema. The fourth phase may occur several weeks after ingestion and is characterized by gastrointestinal obstruction and possibly late hepatic damage.
Overdosage of ferrous salts is particularly dangerous to young children.

Treatment consists of gastric lavage followed by the introduction of 5g desferrioxamine into the stomach. Serum iron levels should be monitored and in severe cases iv desferrioxamine should be given together with supportive and symptomatic measures as required. Gastric lavage with 5% sodium bicarbonate and saline cathartics (e.g. sodium sulphate 30g for adults); milk and eggs with 5g bismuth carbonate every hour as demulcents. Blood or plasma transfusion for shock, oxygen for respiratory embarrassment. Chelating agents (e.g. disodium calcium edetate) may be tried (500mg/500ml by continuous iv infusion). Dimercaprol should not be used since it forms a toxic complex with iron. Desferrioxamine is a specific iron chelating agent and severe acute poisoning in infants should always be treated with desferrioxamine at a dose of 90 mg/kg im followed by 15mg/kg per hour iv until the serum iron is within the plasma binding capacity.

Folic acid
No cases have been reported; but even extremely high doses are unlikely to cause harm to the recipient.

Cyanocobalamin
There are no reports of vitamin B12 overdosage in the literature.

Ascorbic acid
There are no reports of vitamin C overdosage in the literature.

Zinc
In acute overdosage zinc salts are corrosive, due to the formation of zinc chloride by stomach acid; treatment consists of giving milk or alkali carbonates and activated charcoal. The use of emetics or gastric lavage should be avoided.

5. PHARMACOLOGICAL PROPERTIES 1, 2, 3, 4, 5, 6, 7, 8, 15

5.1 Pharmacodynamic properties

Iron
Iron is an essential trace mineral in human nutrition. It is involved in the entire process of respiration, including oxygen transport and electron transport. The principal goal of respiration is the production of biologic energy. Iron is necessary for the production of hemoglobin. Iron-deficiency, which can lead to a microcytic, hypochromic anemia, Nutrient requirements increase during pregnancy to support fetal growth and maternal health. Iron requirements of pregnant women are approximately double that of non-pregnant women because of increased blood volume during pregnancy, increased needs of the fetus, and blood losses that occur during delivery. If iron intake does not meet increased requirements, iron deficiency anemia can occur. The major activity of supplemental iron is in the prevention and treatment of iron deficiency anemia.
Iron has putative immune-enhancing, anticarcinogenic and cognition-enhancing activities.

Folic acid

Folate cofactors play a key role in the *de novo* synthesis of purines and pyrimidines and folate deficiency has been associated with megaloblastic anemia, neural tube defects, cardiovascular disease and predisposition to cancer.
In man, an exogenous source of folate is required for nucleoprotein synthesis and the maintenance of normal erythropoiesis. Folic acid is not metabolically active as such, but is the precursor of tetrahydrofolic acid which is involved as a cofactor for 1-carbon transfer reactions in the biosynthesis of purines and thymidylates of nucleic acids.
Impairment of thymidylate synthesis in patients with folic acid deficiency is thought to account for the defective DNA synthesis that leads to megaloblast formation and megaloblastic and macrocytic anemias. Folate is involved in amino acid interconversions.
Animal and epidemiologic studies have shown that folate deficiency is associated with defects of neural tube closure. Human studies have shown that folic acid, when taken by women planning to become pregnant, can greatly reduce the risk of bearing a child with spina bifida or other neural tube defects. The exact mechanism by which folic acid reduces the risk of neural tube defects and possibly other types of birth defects is not known. It is likely that this effect of folic acid is due to its role in nucleic acid synthesis and/or its role in the metabolism of homocysteine to methionine. Folic acid lowers the
risk of neural tube defects and possibly other types of birth defects.
It may also have antiatherogenic, anticarcinogenic, neuroprotective and antidepressant
actions.

Cyanocobalamin

Vitamin B12 is present in the body mainly as methylcobalamin, adenosylcobalamin and hydroxocobalamin. These act as co-enzymes in the trans methylation of homocysteine to methionine; in the isomerization of methylmalonyl co-enzyme to succinyl co-enzyme and with folate in several metabolic pathways respectively.
Vitamin B12 is used in the treatment of B12 deficiency states, including megaloblastic anemia. It may have antiatherogenic, neuroprotective, anticarcinogenic and detoxifying activities. B12 has putative anti-allergic and mood-modulatory activities.

Ascorbic acid

Ascorbic acid reduces ferric salts to the ferrous form and thus enhances the absorption of non-heme iron.

Vitamin C has antioxidant activity. It may also have anti-atherogenic, anticarcinogenic, antihypertensive, antiviral, antihistaminic, immunomodulatory, opthalmoprotective and airway-protective actions. Vitamin C may aid in the detoxification of some heavy metals, such as lead and other toxic chemicals.

Zinc

Zinc is an essential element in human and animal nutrition with a wide range of biological roles.

Zinc plays catalytic, structural or regulatory roles in the more than 200 zinc metalloenzymes that have been identified in biological systems. These enzymes are involved in nucleic acid and protein metabolism and the production of energy, among other things. Zinc plays a structural role in the formation of the so-called zinc fingers.
Zinc fingers are exploited by transcription factors for interacting with DNA and regulating the activity of genes. Another structural role of zinc is in the maintenance of the integrity of biological membranes resulting in their protection against oxidative injury, among other things. Zinc plays an important role in protein synthesis and in cell division. Zinc deficiency is associated with anemia, short stature, hypogonadism, impaired wound healing, and geophagia.

Zinc deficiency has been shown to increase erythrocyte fragility and alter erythrocyte membrane fluidity.

5.2 Pharmacokinetic properties
Iron
Absorption is increased when iron stores are depleted or red blood cell production is increased. Conversely, high iron blood concentrations decrease absorption. In iron- deficient individuals 20- 30% of ingested iron is absorbed, the amount being approximately proportional to the degree of deficiency. In non-iron-deficient individuals, 3- 10% of ingested iron is absorbed. Absorption occurs principally in the duodenum and proximal jejunum. Absorption is most efficient when iron is ingested in its ferrous rather than ferric form, on an empty stomach. Heme iron is readily absorbed. Non-heme iron is less available and its decreased absorption is further affected by other foods ingested.
Ascorbic acid, as a supplement or in foods, reduces ferric salts to the ferrous form and thus enhances the absorption of non-heme iron.
Hepatocytes and the reticuloendothelial system are the primarily site of iron stores in the body, with some storage in muscle. Iron binds with protein (very high, ≥90%), hemoglobin (high), myoglobin, enzymes, transferrin, ferritin and hemosiderin (low).
No physiological system of elimination exists for iron, and it can accumulate in the body to toxic amount; however, small amount are lost in the shedding of skin, hair and nails; and in feces, perspiration, breast milk (0.5-1.0 mg/day), menstrual blood and urine.

Folic acid
Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Dietary folates are stated to have about half the bioavailability of crystalline folic acid. The naturally occurring folate polyglutamates are largely deconjugated, and then reduced by dihydrofolate reductase in the intestines to form 5-methyltetrahydrofolate, which appears in the portal circulation, where it is extensively bound to plasma proteins. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate

reductase. It is converted to the metabolically active form 5-methyltetrahydrofolate in the plasma and liver.
The principal storage site of folate is the liver; it is also actively concentrated in the CSF.
Folate undergoes enterohepatic circulation. Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folate is distributed into breast milk. Folic acid is removed by hemodialysis.

Cyanocobalamin
Vitamin B12 substances bind to intrinsic factor; a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically.
Vitamin B12 is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Vitamin B12 is stored in the liver, excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Vitamin B12 diffuses across the placenta and also appears in breast milk.

Ascorbic acid
Ascorbic acid is readily absorbed from the gastrointestinal tract and is widely distributed in the body tissues. Plasma concentrations of ascorbic acid rise as the dose ingested is increased until a plateau is reached with doses of about 90 to 150 mg daily. Body stores of ascorbic acid in health are about 1.5 g although more may be stored at intakes above 200 mg daily. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. In deficiency states the concentration in leucocytes declines later and at a slower rate, and has been considered to be a better criterion for the evaluation of deficiency than the concentration in plasma.
Ascorbic acid is reversibly oxidized to dehydroascorbic acid; some is metabolized to ascorbate-2-sulfate, which is inactive, and oxalic acid which are excreted in the urine.
Ascorbic acid in excess of the body's needs is also rapidly eliminated unchanged in the urine; this generally occurs with intakes exceeding 100 mg daily. Ascorbic acid crosses the placenta and is distributed into breast milk. It is removed by hemodialysis.

Zinc
Absorption of zinc from the gastrointestinal tract is incomplete, and is reduced in the presence of some dietary constituents such as phytates.
Bioavailability of dietary zinc varies widely between different sources, but is

about 20 to 30%. Zinc is distributed throughout the body with the highest concentrations found in muscle, bone, skin, eye, and prostatic fluids. It is primarily excreted in the feces, and regulation of fecal losses is important in zinc homoeostasis. Small amounts are lost in urine and perspiration.

5.3 Preclinical safety data 1, 10, 16

Iron

A number of studies have reported that supplementary iron added to the diet enhances the development of neoplasia in animals that produce spontaneous tumors, are inoculated with tumor cells, or are exposed to chemical carcinogens. However, high-level (1200– 1500 mg/kg bw/day) dietary carbonyliron supplementation had no effect on the initiation or promotion of hepatocarcinoma in the Solt-Farber model of hepatocarcinogenesis in rats. There appear to have been relatively few studies carried out to assess the effects of dietary iron overload, in the absence of chemical carcinogens, on tumourigenesis in experimental animals. Supplementation of the diet with 80 mg/kg bw/day iron in mice fed a high-fat diet was associated with increased mitotic and labeling indices in colonic crypts, but low-level dietary iron supplementation in rats (approximately 5.1 mg/kg bw/day iron, for 5 days) was associated with a significantly increased frequency of colonic crypt cell mitoses. Supplementation of BALB/cJ mice with levels of carbonyl-iron up to 4,500 mg/kg bw/day, for periods of up to 12 months, was not associated with the development of hepatic fibrosis or hepatocellular carcinoma, although there was evidence of nuclear changes in hepatocytes in the animals receiving the highest dose supplement for 12 months.

The majority of ferric and ferrous iron salts that have been assessed, and also carbonyl iron, have produced negative results in gene mutation assays, but were positive for viral-enhanced cell transformation in Syrian hamster embryo cells, in vitro, or in a mouse lymphoma assay.

A multigeneration study in rats showed no adverse effects of 20 mg/kg bw/week maternal iron supplementation (by intramuscular injection, but not during pregnancy) on the numbers of offspring produced or their growth weights, with no significant evidence of excess iron transfer across the placenta. A study of maternal iron poisoning in an ovine model also showed that extremely elevated maternal serum iron concentrations were not accompanied by corresponding increases in fetal serum iron levels.

One study showed that iron gluconate was teratogenic after intraperitoneal administration to pregnant mice on the 8th and 9th days of gestation, the most pronounced defect being exencephaly.

Folic acid

Toxicity has been observed in rats given huge doses of folate but this is not found in man at the doses recommended.

Cyanocobalamin

There is no evidence suggesting that vitamin B12 is carcinogenic or genotoxic in vitro or in vivo. However, although data are not consistent, there is some limited evidence to suggest that high doses of vitamin B12 may have tumor promoting activity.

Ascorbic acid
Vitamin C has not been shown to be mutagenic or carcinogenic.

Zinc
Zinc has been found to give positive results in some in vitro and in vivo genotoxicity tests. No data have been identified on the carcinogenicity of zinc.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose,
light liquid paraffin,
colloidal anhydrous silica,
purified talc
magnesium stearate.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from moisture

6.5 Nature and contents of container

Ranferon Capsules are available as PVC blister packs of 10 capsules

6.6 Special precautions for disposal and other handling

No special requirement

7 MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Sun Pharmaceutical Industries Limited

8. MARKETING AUTHORISATION NUMBER

10829

9. DATE OF FIRST REGISTRATION / RENEWAL OF THE REGISTRATION

10. DATE OF REVISION OF THE TEXT

March 2024